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Session M06: Molecular Predictors and Prognosticators

M06-01 Molecular Predictors and Prognosticators, Mon, Sept 3, 10:30 - 12:00

The predictive and prognostic roles of ERCC1 Expression and Akin DNA repair genes in non-small-cell lung cancer

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Cisplatin doublets remain the standard treatment for stage IV non-small-cell lung cancer (NSCLC) patients. Large randomized studies have demonstrated the equivalence of several cisplatin doublets, including gemcitabine and docetaxel, with meager response rates and gloomy survival outcomes, with median survival commonly less than one year(1). Intriguingly, response varied significantly between individual patients(2), highlighting the need for molecular predictive markers for cisplatin and docetaxel response and survival in NSCLC.

NER, a highly versatile pathway for DNA damage removal, is often dysfunctional in NSCLC and could therefore be the Achilles heel for customizing chemotherapy. NER removes numerous types of DNA helix-distorting lesions, including cisplatin- and ultraviolet-induced photo products(3). NER functions by a "cut-and-paste" mechanism in which cisplatin damage recognition, local opening of the DNA helix around the lesion, damage excision and gap-filling occur in successive steps(3) (Figure). NER is composed of two sub-pathways: global genome NER (GG-NER) and transcription-coupled NER (TC-NER) share the same core mechanism but differ in the way lesions are recognized. The structure-specific endonuclease excision repair cross-complementing 1 (ERCC1) performs an essential late step in the NER process, where it nicks the damaged DNA strand at the 5' site of the helix-distorting cisplatin lesion. Importantly, the ERCC1/XPF structure-specific nuclease has an additional role in the repair of cisplatin adducts besides its function in NER: the recombinational repair of interstrand cross-links(4). Moreover, co-localization of ERCC1 foci and RAD51 foci in response to cisplatin treatment has recently been found and may represent recruitment of ERCC1/XPF to sites of recombination repair(5). Previous studies have shown that BRCA1, involved in homologous recombination repair, also plays a major role in the repair of cisplatin DNA damage(6).

High tumor tissue levels of ERCC1 mRNA in ovarian and gastric cancer patients have been associated with cisplatin resistance(7, 8). Similarly, inhibition of ERCC1 expression has been significantly associated with reduced HCR of cisplatin-treated cells and their increased cisplatin sensitivity(9, 10). Cisplatin resistance in NSCLC cell lines has also been related to the increase of HCR(11), and significant differences in survival were observed in cisplatin-treated NSCLC patients according to their DRC(12). When intratumoral ERCC1 mRNA derived from paraffin-embedded tumor specimens was measured by real-time reverse transcriptase polymerase chain reaction (RT-PCR) in metastatic colon cancer patients treated with oxaliplatin and 5-fluorouracil (5-FU), high levels of ERCC1 significantly correlated with poor response and shorter survival(13). We observed longer survival and a trend toward improved response in gemcitabine/cisplatin-treated stage IV NSCLC patients with low ERCC1 mRNA levels(14). A higher response rate was observed in locally advanced NSCLC patients with low levels of ribonucleotide reductase subunit M1 (RRM1) and ERCC1 treated with induction gemcitabine/carboplatin(15). ERCC1 protein expression by immunostaining was associated with survival in NSCLC patients treated with cisplatin-based adjuvant therapy(16).

However, GG-NER, might not correctly detect cisplatin DNA adducts, since it has been shown to possess a low affinity for these adducts(17, 18). On the other hand, defects in TC-NER (Figure) render cells markedly hypersensitive to cisplatin(19). BRCA1-deficient cells are hypersensitive to cisplatin(20).

From August 2001 to October 2005, 444 stage IV NSCLC patients were enrolled in a Spanish Lung Cancer Group randomized trial of customized chemotherapy based on ERCC1 mRNA levels. Patients in the control arm received docetaxel plus cisplatin. Patients in the genotypic arm received treatment based on ERCC1 mRNA levels: those with low levels received docetaxel plus cisplatin; those with high levels received non-cisplatin-based treatment (docetaxel plus gemcitabine). The primary endpoint was the overall objective response rate. Of the 444 patients enrolled in the study, 78 patients (17.6%) went off-study prior to receiving one cycle of chemotherapy. The main reason for withdrawal was insufficient tumor tissue for ERCC1 mRNA assessment. Objective response was 39.3% in the control arm and 50.7% in the genotypic arm (P = .019). This study shows that assessment of ERCC1 mRNA expression is feasible in the clinical setting and predicts response to docetaxel plus cisplatin. Further studies are warranted to refine a multi-biomarker profile predictive of patient outcome.

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M06-02 Molecular Predictors and Prognosticators Mon, Sept 3, 10:30 - 12:00

RRM1 - a predictive and prognostic marker for patients with NSCLC

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RRM1 is the regulatory subunit of ribonucleotide reductase. It is crucial for DNA synthesis and damage repair. In addition, high levels of RRM1 are associated with G2 cell cycle arrest and increased apoptosis *in vitro*. To assess its prognostic utility on lung cancer outcome in patients with complete surgical resection of NSCLC, we analyzed its level of expression by real-time quantitative RTPCR in prospectively collected fresh-frozen tumor specimens and independently in formalin-fixed and paraffin-embedded (FFPE) tumor specimens by quantitative *in situ* fluorescence immunohistochemistry (AQUA). We found that RRM1 expression was directly correlated with survival; i.e., high levels of expression were prognostic of long survival. mRNA and protein expression levels of RRM1 were modestly but significantly correlated (JCO 22:1878, 2004; NEJM 356:800, 2007). Prior retrospective studies had suggested that patients with advanced stage NSCLC and high tumoral RRM1 levels that received gemcitabine-based double agent chemotherapy did worse than those with low RRM1 levels. This paradox has been explored through molecular biological studies in recent years. The results of these studies, which have been conducted in NSCLC (Cancer Res 64:3761, 2004; JCO 24:4731, 2006), colorectal cancer (Cancer Res 65:9510, 2005), and pancreatic cancer (Int J Cancer 120:1355, 2007) by independent laboratories around the world have unequivocally demonstrated that RRM1 is the dominant molecular determinant of gemcitabine efficacy *in vitro*, in experimental animals, and in patients. Thus RRM1 expression in lung cancer patients is a prognostic marker; i.e., high levels are associated with good outcome independent of therapy; and a predictive marker; i.e., high levels are associated with resistance to therapy that is gemcitabine-based. Prospective multi-institutional clinical trials have been initiated with the goal to utilize this knowledge for therapeutic decision making.

M06-03 Molecular Predictors and Prognosticators Mon, Sept 3, 10:30 - 12:00

Prediction of benefit from EGFR TKIs by proteomic analysis of pretreatment serum

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Unlike some tumor types, the majority of the common solid tumors appear not to be driven by single dominant targetable pathways. Instead, diseases such as lung cancer are likely to be much more complex and heterogeneous, with many distinct and overlapping subsets of tumors within the class, each of which will demand an in depth analysis to define the optimal therapeutic approach. These groups are starting to be defined by multiple technologies, and the simplest example is the small subset of patients with tumors expressing mutant EGFR, who achieve substantial clinical benefit from minimally toxic targeted therapy. Even for this small subset of patients with mutant epidermal growth factor receptors (EGFR), multiple resistance mechanisms have emerged requiring different salvage strategies. There also appears to be a group of patients without EGFR mutations who experience clinically significant

